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Hunter-McAlpine Craniosynostosis Phenotype Associated With Skeletal Anomalies and Interstitial Deletion of Chromosome 17q

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Hunter-McAlpine syndrome is an autosomal dominant disorder consisting of variable manifestations including craniosynostosis, almond-shaped palpebral fissures, small mouth, mild acral-skeletal anomalies, short stature, and mental deficiency. We report on a 9-year-old boy with this phenotype with more severe skeletal abnormalities than previously described. Chromosomes showed del(17)(q23.1→q24.2); the more severe phenotype may be explained by the deletion. The deletion also suggests the possibility that the gene for Hunter-McAlpine syndrome might map to that region.

KEY WORDS: craniostenosis, skeletal defects, deletion, mental retardation

INTRODUCTION

Hunter-McAlpine syndrome is an autosomal dominant disorder of craniosynostosis, mental deficiency, almond-shaped palpebral fissures, downturned mouth, mild acral-skeletal anomalies, and short stature. Hunter et al. [1977] first described the syndrome in 1977 in six individuals in one family. Subsequently, Van Maldergem et al. [1990] and Adès et al. [1993] reported three additional patients. Here, we report on an affected 9-year-old boy who also had an interstitial deletion of 17q.

CLINICAL REPORT

The patient (Figs. 1–3) was referred at nearly 9 years for evaluation of multiple congenital anomalies and mental retardation. He was a 3.18 kg, 41.5 cm product of a term, vaginal delivery, born to a 22-year-old G_2P_2 white woman. Pregnancy was complicated by chronic sinusitis, flu-like illness during the second trimester, and abdominal pain during the third trimester. Fetal movement was noted to be active. Labor and delivery were complicated by hypotonic uterine dysfunction. The patient was hospitalized for 6 days after birth due to amniotic aspiration requiring oxygen for approximately 3 or 4 days. The mother and father were normal and the patient had a normal sister.

At birth, the patient was noted to have preaxial polydactyly of his right hand, clubfoot, and facial anomalies. At 4 months, craniosynostoses of the coronal, metopic, and lambdoid sutures were noted. Multiple operations were carried out between 7½ months to 7½ years including craniectomies, multipli-staged craniofacial reconstructions, surgical removal of the extra digit, inguinal hernia repair, right orchidopexy, tonsillectomy/adenoidectomy, surgical clipping for ankyloglossia, and bilateral femoral and proximal tibial hemiepiphysiodesis.

Fig. 1. Propositus at 1 yr.

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Fig. 2. Older child with Hunter-McAlpine syndrome. Compare face with Figure 1 (from Cohen [1986]).

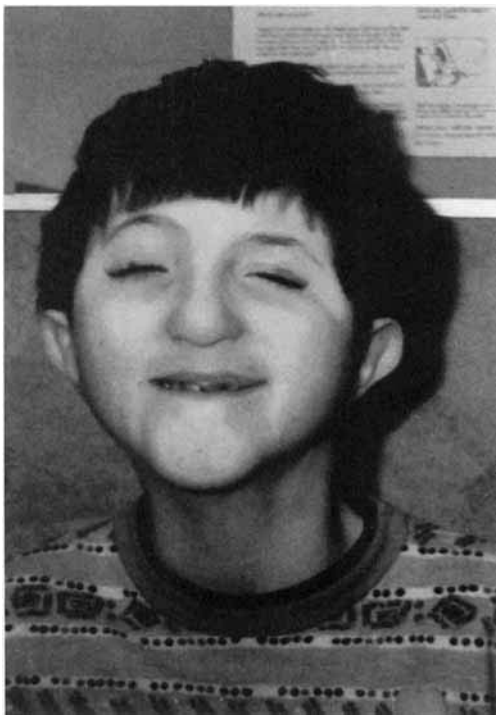

Fig. 3. Propositus at 8 11/12 years. Triangular face. He had multiple cranial and craniofacial procedures from the ages of 7½ months to 7½ years.

Radiographic examination showed a bifid right first metacarpal with a single proximal phalanx in the thumb and two distal phalanges, capitate-hamate fusion, and small irregular middle phalangeal epiphyses. The quotient of the distal first phalanx to the fifth metacarpal was significantly below the mean (0.24; mean 0.44 ± 0.02). He was also noted to have hyperopia, strabismus, esotropia, and amblyopia and a history of sinusitis, possible seizure activity, and scoliosis.

On physical examination at 8 11/12 years, height was approximately at the 30th centile, weight, ~25th centile, and head circumference (OFC), ~10th centile. Manifestations included triangular-shaped face (Fig. 3), short palpebral fissures, small mouth with a thin vermilion border of the upper lip, highly arched palate, malocclusion, dental anomalies, prominent chin, and apparently low-set and simplified ears. He also had limited extension and flexion of fingers, elbows, shoulders, and knees; limited rotation at the elbows; coxa valga and genua valga; and clinodactyly of the fifth toes.

Developmental delays were first noted when he was approximately 2½ months of age. At 8 5/12 years, he was functioning at about a 3-year level. Chromosomes showed del(17)(q23.1→q24.2) (Fig. 4).

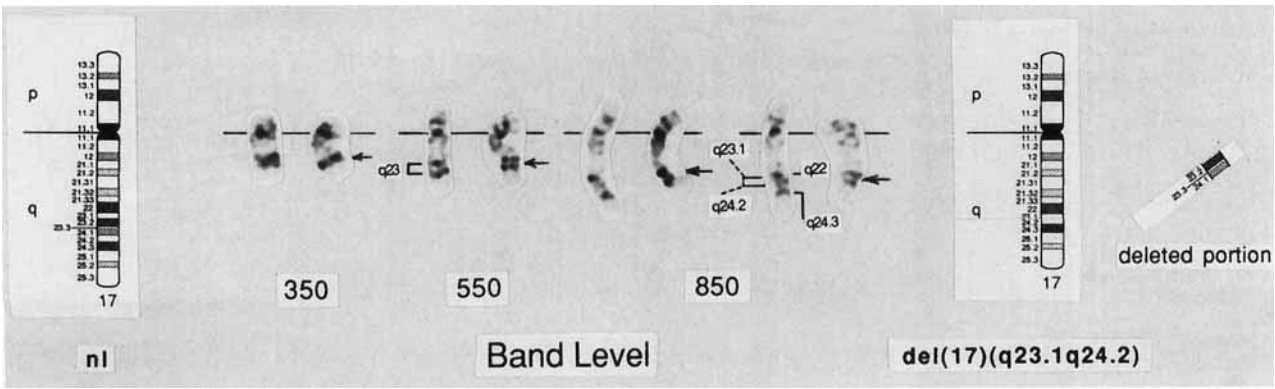

Fig. 4. Examples of chromosome 17 homologues at various levels of chromosome condensation. Arrows indicate deleted region.

TABLE I. Clinical Manifestations of Hunter-McAlpine Syndrome

Manifestations	Hunter et al., 1977	Van Maldergem et al., 1990	Adès et al., 1993	Our case
Growth				
Short stature	3/6	+	3rd–10th centile	–
Performance				
Mental deficiency	6/6	+	+	+
Visual abnormalities	2/6	–	+	+
Craniofacial				
Microcephaly	2/6	+	+	–
Craniosynostosis	2/6	–	+	+
Almond-shaped eyes	4/6	+	+	–
Long philtrum	1/6	?	+	+
Thin lips	1/6	+	+	+
Downturned mouth	3/6	+	?	–
Dental abnormalities	1/6	+	+	+
Pointed, small chin	2/6	?	?	+
Skeletal				
Joint limitation	1/6	?	+	+
Small hands	1/6	+	?	–
Brachydactyly	1/6	+	+	–
Coned epiphyses	3/6	+	+	+
D1:M5 ratio	4/6	+	+	+
Metacarpal fusion	–	+	+	+
Polydactyly, hand	–	–	–	+
Clubfoot	–	–	–	+
Other				
Cardiac defect	1/6	–	+	–
Inguinal hernia	1/6	+	–	+

TABLE II. Clinical Manifestations of Reported 17q Deletions

Manifestations	Park et al., 1992	Dallapiccola et al., 1993	Khalifa et al., 1993	Leven et al., 1994	Our case
Sex	Female	Male	Male	Female	Male
Karyotype	del(17)(q21.3q23)	del(17)(q21.3q24.2)	del(17)(q21.3q23)	del(17)(q23.2q24.3)	del(17)(q23.1q24.2)
Growth					
Birth weight (g)	2370	2780	3425	1160	3180
Birth length (cm)	47	47	52	36	41.5
Birth OFC (cm)	30.5	33	32	27	?
Height (centile)	<2nd	?	>95th	<5th	30th
Performance					
Developmental delay	Mild–Mod	?	Mod–severe	?	Mod–severe
Irritability	+	?	+	?	?
Poor feeder	+	?	+	?	?
Cerebral abnormalities	+	+	–	+	?
Seizures	?	+	?	?	Possible
Visual impairment	–	?	+	?	+
Hearing loss	–	?	+	?	–
Craniofacial					
Microcephaly	+	+	+	–	–
Craniosynostosis	–	–	–	–	+
Facial shape	Round	Round	Round	?	Triangular
Hypertelorism	+	+	?	+	+
Upslanting palpebral fissures	+	+	+	–	–
Broad nasal root	?	?	+	Flat nasal bridge	+
Anteverted nares	+	+	?	–	–
Long philtrum	+	+	–	Hypoplastic	+
Downturned mouth	+	?	?	?	–
Bifid uvula/cleft palate	+	+	–	+	–
Micrognathia	+	±	+	?	+
Ear anomalies	+	–	+	+	–
Skeletal					
Hip dislocation	–	–	+	Probable	–
Clubfoot	+	–	–	–	+
Proximally placed thumbs	+	+	+	+	+
Symphalangism	+	+	+	?	+
Peripheral skeletal anomalies	?	?	?	+	+
Other					
Congenital heart defect	–	+	–	+	–
Tracheoesophageal fistula	+	+	–	?	–
Cryptorchidism	–	–	+	–	+
Inguinal hernia	–	–	+	?	+

DISCUSSION

Table I compares our patient's manifestations with those of additionally reported cases. Although similar to previously described patients, he has more severe skeletal involvement, particularly multiple synostoses, significant limitation of motion in both large and small joints, and distal limb anomalies including preaxial polydactyly and two phalanges in the distal portion of the right thumb. Significantly absent in our patient was short stature. The facial appearance of our patient is strikingly like that of other affected patients (Figs. 1, 2).

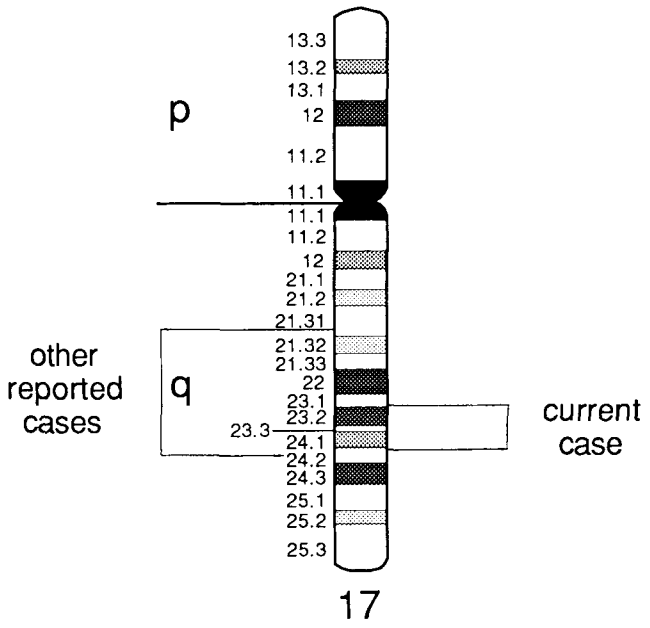

Fig. 5. Deletion in propositus compared to deleted areas of other reported cases.

Chromosomes in our patient showed del(17)(q23.1→q24.2) (Fig. 4). The more severe skeletal manifestations can probably be explained as "added developmental noise" from involvement of contiguous genes in the deletion. Furthermore, the deletion suggests the possibility that the gene for Hunter-McAlpine syndrome might map to that region. The manifestations of other patients with del(17q) [Park et al., 1992; Dallapiccola et al., 1993; Khalifa et al., 1993; Levin et al., 1994] are compared in Table II and the deletions are shown in Figure 5.

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